**BREVIBLOC - esmolol hydrochloride injection, solution, concentrate**
**BREVIBLOC - esmolol hydrochloride injection**
Baxter Healthcare Corporation

**BREVIBLOC PREMIXED INJECTION**
(Esmolol Hydrochloride)
**2,500 mg/250 mL (10 mg/mL)** Ready-to-use Bags
250 mL Bags
Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride
**For Intravenous Use**
**Can be used for direct intravenous use.**
Esmolol Hydrochloride concentration = 10 milligrams/mL (10,000 micrograms/mL)
**Single Patient Use Only**
**No Preservatives Added**

**BREVIBLOC DOUBLE STRENGTH PREMIXED INJECTION**
(Esmolol Hydrochloride)
**2,000 mg/100 mL (20 mg/mL)** Ready-to-use Bags
100 mL Bags
Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride
**For Intravenous Use**
**Can be used for direct intravenous use.**
Esmolol Hydrochloride concentration = 20 milligrams/mL (20,000 micrograms/mL)
**Single Patient Use Only**
**No Preservatives Added**

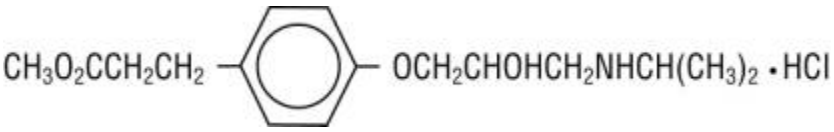
**BREVIBLOC INJECTION**
(Esmolol Hydrochloride)
**100 mg/10 mL (10 mg/mL)** Ready-to-use Vials
10 mL Vials
Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride
**For Intravenous Use**
**Can be used for direct intravenous use.**
Esmolol Hydrochloride concentration = 10 milligrams/mL (10,000 micrograms/mL)
**Single Patient Use Only**
**No Preservatives Added**

**BREVIBLOC DOUBLE STRENGTH INJECTION**
(Esmolol Hydrochloride)
**100 mg/5 mL (20 mg/mL)** Ready-to-use Vials
5 mL Vials
Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride
**For Intravenous Use**
**Can be used for direct intravenous use.**
Esmolol Hydrochloride concentration = 20 milligrams/mL (20,000 micrograms/mL)
**Single Patient Use Only**
**No Preservatives Added**

**BREVIBLOC CONCENTRATE**
(Esmolol Hydrochloride)
**2,500 mg/10 mL (250 mg/mL)** Ampuls for Dilution
10 mL Ampuls
**NOT FOR DIRECT INTRAVENOUS INJECTION.**
Esmolol Hydrochloride concentration = 250 milligrams/mL (250,000 micrograms/mL)
**AMPULS MUST BE DILUTED PRIOR TO INFUSION - SEE DOSAGE AND ADMINISTRATION, Directions for Use of the Brevibloc Concentrate 10 mL Ampul (250 milligrams/mL).**
**Rx only**

## DESCRIPTION

BREVIBLOC (Esmolol Hydrochloride) is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent with a very short duration of action (elimination half-life is approximately 9 minutes). Esmolol Hydrochloride is:
(±)-Methyl p-[2-hydroxy-3-(isopropylamino) propoxy] hydrocinnamate hydrochloride and has the following structure:



Esmolol Hydrochloride has the empirical formula $C_{16}H_{26}NO_4Cl$ and a molecular weight of 331.8. It has one asymmetric center and exists as an enantiomeric pair.
Esmolol Hydrochloride is a white to off-white crystalline powder. It is a relatively hydrophilic compound which is very soluble in water and freely soluble in alcohol. Its partition coefficient (octanol/water) at pH 7.0 is 0.42 compared to 17.0 for propranolol.

### Brevibloc Premixed Injection

BREVIBLOC PREMIXED INJECTION is a clear, colorless to light yellow, sterile, nonpyrogenic, iso-osmotic solution of esmolol hydrochloride in sodium chloride.
**2500 mg, 250 mL Single Use Premixed Bag** – Each mL contains 10 mg Esmolol Hydrochloride, 5.9 mg Sodium Chloride, USP and Water for Injection, USP; buffered with 2.8 mg Sodium Acetate Trihydrate, USP and 0.546 mg Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added, as necessary, to adjust pH to 5.0 (4.5-5.5). The calculated osmolarity is 312 mOsmol/L. The 250 mL bag is a non-latex, non-PVC IntraVia bag with dual PVC ports. The IntraVia bag is manufactured from a specially designed multilayer plastic (PL 2408). Solutions in contact with the plastic container leach out certain chemical compounds from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. SeeDOSAGE AND ADMINISTRATION, Directions for Use of the Premixed Bag for additional information.
**2000 mg, 100 mL Single Use Premixed Bag DOUBLE STRENGTH** – Each mL contains 20 mg Esmolol Hydrochloride, 4.1 mg Sodium Chloride, USP and Water for Injection, USP; buffered with 2.8 mg Sodium Acetate Trihydrate, USP and 0.546 mg Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added, as necessary, to adjust pH to 5.0 (4.5-5.5). The calculated osmolarity is 312 mOsmol/L. The 100 mL bag is a non-latex, non-PVC IntraVia bag with dual PVC ports. The IntraVia bag is manufactured from a specially designed multilayer plastic (PL 2408). Solutions in contact with the plastic container leach out certain chemical compounds from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. See DOSAGE AND ADMINISTRATION, Directions for Use of the Premixed Bag for additional information.

### Brevibloc Injection

BREVIBLOC INJECTION is a clear, colorless to light yellow, sterile, nonpyrogenic, iso–osmotic solution of esmolol hydrochloride in sodium chloride.
**100 mg, 10 mL Single Dose Vial** – Each mL contains 10 mg Esmolol Hydrochloride, 5.9 mg Sodium Chloride, USP and Water for Injection, USP; buffered with 2.8 mg Sodium Acetate Trihydrate, USP and 0.546 mg Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added, as necessary to adjust pH to 5.0 (4.5–5.5).
**100 mg, 5 mL DOUBLE STRENGTH Single Dose Vial** – Each mL contains 20 mg Esmolol Hydrochloride, 4.1 mg Sodium Chloride, USP and Water for Injection, USP; buffered with 2.8 mg Sodium Acetate Trihydrate, USP and 0.546 mg Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added, as necessary to adjust pH to 5.0 (4.5-5.5).

### Brevibloc Concentrate

BREVIBLOC CONCENTRATE is a clear, colorless to light yellow, sterile, nonpyrogenic concentrate.
**2500 mg, 10 mL Ampul** – Each mL contains 250 mg Esmolol Hydrochloride in 25% Propylene Glycol, USP, 25% Alcohol, USP and Water for Injection, USP; buffered with 17.0 mg Sodium Acetate Trihydrate, USP, and 0.00715 mL Glacial Acetic Acid, USP. Sodium Hydroxide and/or Hydrochloric Acid added, as necessary, to adjust pH to 3.5-5.5. NOT FOR DIRECT INTRAVENOUS USE - AMPUL MUST BE DILUTED PRIOR TO INFUSION. See DOSAGE AND ADMINISTRATION, Directions for Use of the Brevibloc Concentrate 10 mL Ampul (250 milligrams/mL).

## CLINICAL PHARMACOLOGY

BREVIBLOC (Esmolol Hydrochloride) is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent with rapid onset, a very short duration of action, and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. Its elimination half-life after intravenous infusion is approximately 9 minutes. BREVIBLOC inhibits the $beta_1$ receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit $beta_2$ receptors located chiefly in the bronchial and vascular musculature.

### Pharmacokinetics and Metabolism

BREVIBLOC (Esmolol Hydrochloride) is rapidly metabolized by hydrolysis of the ester linkage, chiefly by the esterases in the cytosol of red blood cells and not by plasma cholinesterases or red cell membrane acetylcholinesterase. Total body clearance in man was found to be about 20 L/kg/hr, which is greater than cardiac output; thus the metabolism of BREVIBLOC is not limited by

the rate of blood flow to metabolizing tissues such as the liver or affected by hepatic or renal blood flow. BREVIBLOC has a rapid distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes.
Using an appropriate loading dose, steady-state blood levels of BREVIBLOC for dosages from 50-300 mcg/kg/min (0.05-0.3 mg/kg/min) are obtained within five minutes. (Steady-state is reached in about 30 minutes without the loading dose.) Steady-state blood levels of BREVIBLOC increase linearly over this dosage range and elimination kinetics are dose-independent over this range. Steady-state blood levels are maintained during infusion but decrease rapidly after termination of the infusion. Because of its short half-life, blood levels of BREVIBLOC can be rapidly altered by increasing or decreasing the infusion rate and rapidly eliminated by discontinuing the infusion.
Consistent with the high rate of blood-based metabolism of BREVIBLOC, less than 2% of the drug is excreted unchanged in the urine. Within 24 hours of the end of infusion, approximately 73-88% of the dosage has been accounted for in the urine as the acid metabolite of BREVIBLOC.
Metabolism of BREVIBLOC results in the formation of the corresponding free acid and methanol. The acid metabolite has been shown in animals to have about 1/1500th the activity of esmolol and in normal volunteers its blood levels do not correspond to the level of beta blockade. The acid metabolite has an elimination half-life of about 3.7 hours and is excreted in the urine with a clearance approximately equivalent to the glomerular filtration rate. Excretion of the acid metabolite is significantly decreased in patients with renal disease, with the elimination half-life increased to about ten-fold that of normals, and plasma levels considerably elevated.
Methanol blood levels, monitored in subjects receiving BREVIBLOC for up to 6 hours at 300 mcg/kg/min (0.3 mg/kg/min) and 24 hours at 150 mcg/kg/min (0.15 mg/kg/min), approximated endogenous levels and were less than 2% of levels usually associated with methanol toxicity.
BREVIBLOC has been shown to be 55% bound to human plasma protein, while the acid metabolite is only 10% bound.

**Pharmacodynamics**
Clinical pharmacology studies in normal volunteers have confirmed the beta blocking activity of BREVIBLOC (Esmolol Hydrochloride), showing reduction in heart rate at rest and during exercise, and attenuation of isoproterenol-induced increases in heart rate. Blood levels of BREVIBLOC have been shown to correlate with extent of beta blockade. After termination of infusion, substantial recovery from beta blockade is observed in 10–20 minutes.
In human electrophysiology studies, BREVIBLOC produced effects typical of a beta blocker; a decrease in the heart rate, increase in sinus cycle length, prolongation of the sinus node recovery time, prolongation of the AH interval during normal sinus rhythm and during atrial pacing, and an increase in antegrade Wenckebach cycle length.
In patients undergoing radionuclide angiography, BREVIBLOC, at dosages of 200 mcg/kg/min (0.2 mg/kg/min), produced reductions in heart rate, systolic blood pressure, rate pressure product, left and right ventricular ejection fraction and cardiac index at rest, which were similar in magnitude to those produced by intravenous propranolol (4 mg). During exercise, BREVIBLOC produced reductions in heart rate, rate pressure product and cardiac index which were also similar to those produced by propranolol, but produced a significantly larger fall in systolic blood pressure. In patients undergoing cardiac catheterization, the maximum therapeutic dose of 300 mcg/kg/min (0.3 mg/kg/min) of BREVIBLOC produced similar effects and, in addition, there were small, clinically insignificant increases in the left ventricular end diastolic pressure and pulmonary capillary wedge pressure. At thirty minutes after the discontinuation of BREVIBLOC infusion, all of the hemodynamic parameters had returned to pretreatment levels.
The relative cardioselectivity of BREVIBLOC was demonstrated in 10 mildly asthmatic patients. Infusions of BREVIBLOC [100, 200 and 300 mcg/kg/min (0.1, 0.2 and 0.3 mg/kg/min)] produced no significant increases in specific airway resistance compared to placebo. At 300 mcg/kg/min (0.3 mg/kg/min), BREVIBLOC produced slightly enhanced bronchomotor sensitivity to dry air stimulus. These effects were not clinically significant, and BREVIBLOC was well tolerated by all patients. Six of the patients also received intravenous propranolol, and at a dosage of 1 mg, two experienced significant, symptomatic bronchospasm requiring bronchodilator treatment. One other propranolol-treated patient also experienced dry air-induced bronchospasm. No adverse pulmonary effects were observed in patients with COPD who received therapeutic dosages of BREVIBLOC for treatment of supraventricular tachycardia (51 patients) or in perioperative settings (32 patients).

**Supraventricular Tachycardia**
In two multicenter, randomized, double-blind, controlled comparisons of BREVIBLOC (Esmolol Hydrochloride) with placebo and propranolol, maintenance doses of 50 to 300 mcg/kg/min (0.05 to 0.3 mg/kg/min) of BREVIBLOC were found to be more effective than placebo and about as effective as propranolol, 3–6 mg given by bolus injections, in the treatment of supraventricular tachycardia, principally atrial fibrillation and atrial flutter. The majority of these patients developed their arrhythmias postoperatively. About 60-70% of the patients treated with BREVIBLOC had a desired therapeutic effect (either a 20% reduction in heart rate, a decrease in heart rate to less than 100 bpm, or, rarely, conversion to NSR) and about 95% of those who responded did so at a dosage of 200 mcg/kg/min (0.2 mg/kg/min) or less. The average effective dosage of BREVIBLOC was approximately 100-115 mcg/kg/min (0.1-0.115 mg/kg/min) in the two studies. Other multicenter baseline-controlled studies gave essentially similar results. In the comparison with propranolol, about 50% of patients in both the BREVIBLOC and propranolol groups were on concomitant digoxin. Response rates were slightly higher with both beta blockers in the digoxin-treated patients.
In all studies significant decreases of blood pressure occurred in 20-50% of patients, identified either as adverse reaction reports by investigators, or by observation of systolic pressure less than 90 mmHg or diastolic pressure less than 50 mmHg. The hypotension was symptomatic (mainly diaphoresis or dizziness) in about 12% of patients, and therapy was discontinued in about 11% of

patients, about half of whom were symptomatic. In comparison to propranolol, hypotension was about three times as frequent with BREVIBLOC, 53% vs. 17%. The hypotension was rapidly reversible with decreased infusion rate or after discontinuation of therapy with BREVIBLOC. For both BREVIBLOC and propranolol, hypotension was reported less frequently in patients receiving concomitant digoxin.

## INDICATIONS AND USAGE

### Supraventricular Tachycardia

BREVIBLOC (Esmolol Hydrochloride) is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances where short term control of ventricular rate with a short-acting agent is desirable. BREVIBLOC is also indicated in noncompensatory sinus tachycardia where, in the physician's judgment, the rapid heart rate requires specific intervention. BREVIBLOC is not intended for use in chronic settings where transfer to another agent is anticipated.

### Intraoperative and Postoperative Tachycardia and/or Hypertension

BREVIBLOC (Esmolol Hydrochloride) is indicated for the treatment of tachycardia and hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia, and in the postoperative period, when in the physician's judgment such specific intervention is considered indicated.
Use of BREVIBLOC to prevent such events is not recommended.

## CONTRAINDICATIONS

BREVIBLOC (Esmolol Hydrochloride) is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure (see WARNINGS).

## WARNINGS

### Hypotension

In clinical trials 20-50% of patients treated with BREVIBLOC (Esmolol Hydrochloride) have experienced hypotension, generally defined as systolic pressure less than 90 mmHg and/or diastolic pressure less than 50 mmHg. About 12% of the patients have been symptomatic (mainly diaphoresis or dizziness). Hypotension can occur at any dose but is dose-related so that doses beyond 200 mcg/kg/min (0.2 mg/kg/min) are not recommended. Patients should be closely monitored, especially if pretreatment blood pressure is low. Decrease of dose or termination of infusion reverses hypotension, usually within 30 minutes.

### Cardiac Failure

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. Continued depression of the myocardium with beta blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, BREVIBLOC (Esmolol Hydrochloride) should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of BREVIBLOC, specific treatment may also be considered (seeOVERDOSAGE). The use of BREVIBLOC for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium. Despite the rapid onset and offset of the effects of BREVIBLOC, several cases of death have been reported in complex clinical states where BREVIBLOC was presumably being used to control ventricular rate.

### Intraoperative and Postoperative Tachycardia and/or Hypertension

BREVIBLOC (Esmolol Hydrochloride) should not be used as the treatment for hypertension in patients in whom the increased blood pressure is primarily due to the vasoconstriction associated with hypothermia.

### Bronchospastic Diseases

PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity and titratability, BREVIBLOC (Esmolol Hydrochloride) may be used with caution in patients with bronchospastic diseases. However, since $beta_1$ selectivity is not absolute, BREVIBLOC should be carefully titrated to obtain the lowest possible effective dose. In the event of bronchospasm, the infusion should be terminated immediately; a $beta_2$ stimulating agent may be administered if conditions warrant but should be used with particular caution as patients already have rapid ventricular rates.

### Diabetes Mellitus and Hypoglycemia

BREVIBLOC (Esmolol Hydrochloride) should be used with caution in diabetic patients requiring a beta blocking agent. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

## PRECAUTIONS

### General

Infusion concentrations of 20 mg/mL were associated with more serious venous irritation, including thrombophlebitis, than concentrations of 10 mg/mL with BREVIBLOC CONCENTRATE, extravasation of 20 mg/mL or higher may lead to a serious local reaction and possible skin necrosis. Concentrations greater than 10 mg/mL or infusion into small veins or through a butterfly catheter should be avoided.

Because the acid metabolite of BREVIBLOC is primarily excreted unchanged by the kidney, BREVIBLOC (Esmolol Hydrochloride) should be administered with caution to patients with impaired renal function. The elimination half-life of the acid metabolite was prolonged ten-fold and the plasma level was considerably elevated in patients with end–stage renal disease.

Care should be taken in the intravenous administration of BREVIBLOC CONCENTRATE as sloughing of the skin and necrosis have been reported in association with infiltration and extravasation of intravenous infusions.

### Drug Interactions

Catecholamine-depleting drugs, e.g., reserpine, may have an additive effect when given with beta blocking agents. Patients treated concurrently with BREVIBLOC (Esmolol Hydrochloride) and a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

A study of interaction between BREVIBLOC and warfarin showed that concomitant administration of BREVIBLOC and warfarin does not alter warfarin plasma levels. BREVIBLOC concentrations were equivocally higher when given with warfarin, but this is not likely to be clinically important.

When digoxin and BREVIBLOC were concomitantly administered intravenously to normal volunteers, there was a 10-20% increase in digoxin blood levels at some time points. Digoxin did not affect BREVIBLOC pharmacokinetics. When intravenous morphine and BREVIBLOC were concomitantly administered in normal subjects, no effect on morphine blood levels was seen, but BREVIBLOC steady-state blood levels were increased by 46% in the presence of morphine. No other pharmacokinetic parameters were changed.

The effect of BREVIBLOC on the duration of succinylcholine-induced neuromuscular blockade was studied in patients undergoing surgery. The onset of neuromuscular blockade by succinylcholine was unaffected by BREVIBLOC, but the duration of neuromuscular blockade was prolonged from 5 minutes to 8 minutes.

Although the interactions observed in these studies do not appear to be of major clinical importance, BREVIBLOC should be titrated with caution in patients being treated concurrently with digoxin, morphine, succinylcholine or warfarin.

While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Caution should be exercised when considering the use of BREVIBLOC and verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Additionally, BREVIBLOC should not be used to control supraventricular tachycardia in the presence of agents which are vasoconstrictive and inotropic such as dopamine, epinephrine, and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Because of its short term usage no carcinogenicity, mutagenicity or reproductive performance studies have been conducted with BREVIBLOC (Esmolol Hydrochloride).

### Pregnancy

Teratogenic Effects

Pregnancy Category C

Teratogenicity studies in rats at intravenous dosages of BREVIBLOC (Esmolol Hydrochloride) up to 3000 mcg/kg/min (3 mg/kg/min) (ten times the maximum human maintenance dosage) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while a dosage of 10,000 mcg/kg/min (10 mg/kg/min) produced maternal toxicity and lethality. In rabbits, intravenous dosages up to 1000 mcg/kg/min (1 mg/kg/min) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while 2500 mcg/kg/min (2.5 mg/kg/min) produced minimal maternal toxicity and increased fetal resorptions.

Although there are no adequate and well-controlled studies in pregnant women, use of esmolol in the last trimester of pregnancy or during labor or delivery has been reported to cause fetal bradycardia, which continued after termination of drug infusion. BREVIBLOC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Nursing Mothers

It is not known whether BREVIBLOC (Esmolol Hydrochloride) is excreted in human milk; however, caution should be exercised when BREVIBLOC is administered to a nursing woman.

**Pediatric Use**
The safety and effectiveness of BREVIBLOC (Esmolol Hydrochloride) in pediatric patients have not been established.

## ADVERSE REACTIONS
The following adverse reaction rates are based on use of BREVIBLOC (Esmolol Hydrochloride) in clinical trials involving 369 patients with supraventricular tachycardia and over 600 intraoperative and postoperative patients enrolled in clinical trials. Most adverse effects observed in controlled clinical trial settings have been mild and transient. The most important adverse effect has been hypotension (seeWARNINGS). Deaths have been reported in post-marketing experience occurring during complex clinical states where BREVIBLOC was presumably being used simply to control ventricular rate (see WARNINGS, Cardiac Failure).

**Cardiovascular**
Symptomatic hypotension (diaphoresis, dizziness) occurred in 12% of patients, and therapy was discontinued in about 11%, about half of whom were symptomatic. Asymptomatic hypotension occurred in about 25% of patients. Hypotension resolved during BREVIBLOC (Esmolol Hydrochloride) infusion in 63% of these patients and within 30 minutes after discontinuation of infusion in 80% of the remaining patients. Diaphoresis accompanied hypotension in 10% of patients. Peripheral ischemia occurred in approximately 1% of patients. Pallor, flushing, bradycardia (heart rate less than 50 beats per minute), chest pain, syncope, pulmonary edema and heart block have each been reported in less than 1% of patients. In two patients without supraventricular tachycardia but with serious coronary artery disease (post inferior myocardial infarction or unstable angina), severe bradycardia/sinus pause/asystole has developed, reversible in both cases with discontinuation of treatment.

**Central Nervous System**
Dizziness has occurred in 3% of patients; somnolence in 3%; confusion, headache, and agitation in about 2%; and fatigue in about 1% of patients. Paresthesia, asthenia, depression, abnormal thinking, anxiety, anorexia, and lightheadedness were reported in less than 1% of patients. Seizures were also reported in less than 1% of patients, with one death.

**Respiratory**
Bronchospasm, wheezing, dyspnea, nasal congestion, rhonchi, and rales have each been reported in less than 1% of patients.

**Gastrointestinal**
Nausea was reported in 7% of patients. Vomiting has occurred in about 1% of patients. Dyspepsia, constipation, dry mouth, and abdominal discomfort have each occurred in less than 1% of patients. Taste perversion has also been reported.

**Skin (Infusion Site)**
Infusion site reactions including inflammation and induration were reported in about 8% of patients. Edema, erythema, skin discoloration, burning at the infusion site, thrombophlebitis, and local skin necrosis from extravasation have each occurred in less than 1% of patients.

**Miscellaneous**
Each of the following has been reported in less than 1% of patients: Urinary retention, speech disorder, abnormal vision, midscapular pain, rigors, and fever.

## OVERDOSAGE

**Acute Toxicity**
Overdoses of BREVIBLOC (Esmolol Hydrochloride) can cause cardiac arrest. In addition, overdoses can produce bradycardia, hypotension, electromechanical dissociation and loss of consciousness. Cases of massive accidental overdoses of BREVIBLOC have occurred due to dilution errors. Use of BREVIBLOC PREMIXED INJECTION and BREVIBLOC DOUBLE STRENGTH PREMIXED INJECTION may reduce the potential for dilution errors. Some of these overdoses have been fatal while others resulted in permanent disability. Bolus doses in the range of 625 mg to 2.5 g (12.5–50 mg/kg) have been fatal. Patients have recovered completely from overdoses as high as 1.75 g given over one minute or doses of 7.5 g given over one hour for cardiovascular surgery. The patients who survived appear to be those whose circulation could be supported until the effects of BREVIBLOC resolved. Because of its approximately 9-minute elimination half-life, the first step in the management of toxicity should be to discontinue the BREVIBLOC infusion. Then, based on the observed clinical effects, the following general measures should also be considered.
**Bradycardia:** Intravenous administration of atropine or another anticholinergic drug.
**Bronchospasm:** Intravenous administration of a $beta_2$ stimulating agent and/or a theophylline derivative.
**Cardiac Failure:** Intravenous administration of a diuretic and/or digitalis glycoside. In shock resulting from inadequate cardiac contractility, intravenous administration of dopamine, dobutamine, isoproterenol, or amrinone may be considered.
**Symptomatic Hypotension:** Intravenous administration of fluids and/or pressor agents.

**DOSAGE AND ADMINISTRATION**

**Dosing Information:**

SUPRAVENTRICULAR TACHYCARDIA
Dosage needs to be titrated, using ventricular rate as the guide.

An initial loading dose of 0.5 milligrams/kg (500 micrograms/kg) infused over a minute duration followed by a maintenance infusion of 0.05 milligrams/kg/min (50 micrograms/kg/min) for the next 4 minutes is recommended. This should give a rough guide with respect to the responsiveness of ventricular rate.

After the 4 minutes of initial maintenance infusion (total treatment duration being 5 minutes), depending upon the desired ventricular response, the maintenance infusion may be continued at 0.05 mg/kg/min or increased step-wise (e.g. 0.1 mg/kg/min, 0.15 mg/kg/min to a maximum of 0.2 mg/kg/min) with each step being maintained for 4 or more minutes.

If more rapid slowing of ventricular response is imperative, the 0.5 mg/kg loading dose infused over a 1 minute period may be repeated, followed by a maintenance infusion of 0.1 mg/kg/min for 4 minutes. Then, depending upon ventricular rate, another (and final) loading dose of 0.5 mg/kg/min infused over a 1 minute period may be administered followed by a maintenance infusion of 0.15 mg/kg/min. If needed, after 4 minutes of the 0.15 mg/kg/min maintenance infusion, the maintenance infusion may be increased to a maximum of 0.2 mg/kg/min.

In the absence of loading doses, constant infusion of a single concentration of esmolol reaches pharmacokinetic and pharmacodynamic steady-state in about 30 minutes. Maintenance infusions (with or without loading doses) may be continued for as long as 24 hours.

The following table summarizes the above and assumes that 3 loading doses (the maximum recommended) are infused over 1 minute and incremental maintenance doses are required after each loading dose. There should be no 4th loading dose, but the maintenance dose may be incremented one more time.

| **Elapsed Time** | **Loading Dose** (over 1 minute) | | **Maintenance Dose** (over 4 minutes) | |
|---|---|---|---|---|
| (minutes) | micrograms/kg/min | milligrams/kg/min | micrograms/kg/min | milligrams/kg/min |
| 0 – 1 | 500 | 0.5 | | |
| 1 – 5 | | | 50 | 0.05 |
| 5 – 6 | 500 | 0.5 | | |
| 6 – 10 | | | 100 | 0.1 |
| 10 – 11 | 500 | 0.5 | | |
| 11 – 15 | | | 150 | 0.15 |
| 15 – 16 | · | · | | |
| 16 – 20 | | | *200 | *0.2 |
| > 20 | | | Maintenance dose titrated to heart rate or other clinical endpoint. | |

*****As the desired heart rate or endpoint is approached, the loading infusion may be omitted and the maintenance infusion titrated to 300 mcg/kg/min (0.3 mg/kg/min) or downward as appropriate. Maintenance dosages above 200 mcg/kg/min (0.2 mg/kg/min) have not been shown to have significantly increased benefits. The interval between titration steps may be increased.

In the treatment of supraventricular tachycardia, responses to BREVIBLOC (Esmolol Hydrochloride) usually (over 95%) occur within the range of 50 to 200 micrograms/kg/min (0.05 to 0.2 milligrams/kg/min). The average effective dosage is approximately 100 micrograms/kg/min (0.1 milligrams/kg/min) although dosages as low as 25 micrograms/kg/min (0.025 milligrams/kg/min) have been adequate in some patients. Dosages as high as 300 micrograms/kg/min (0.3 milligrams/kg/min) have been used, but these provide little added effect and increase the rate of adverse effects, so doses greater than 200 micrograms/kg/min are not recommended. Dosage of BREVIBLOC in supraventricular tachycardia must be individualized by titration in which each step consists of a loading dosage followed by a maintenance dosage.

This specific dosage regimen has not been studied intraoperatively and, because of the time required for titration, may not be optimal for intraoperative use.

The safety of dosages above 300 mcg/kg/min (0.3 mg/kg/min) has not been studied.

In the event of an adverse reaction, the dosage of BREVIBLOC may be reduced or discontinued. If a local infusion site reaction develops, an alternate infusion site should be used and caution should be taken to prevent extravasation. The use of butterfly needles should be avoided.

Abrupt cessation of BREVIBLOC in patients has not been reported to produce the withdrawal effects which may occur with abrupt withdrawal of beta blockers following chronic use in coronary artery disease (CAD) patients. However, caution should still be used in abruptly discontinuing infusions of BREVIBLOC in CAD patients.

After achieving an adequate control of the heart rate and a stable clinical status in patients with supraventricular tachycardia, transition to alternative antiarrhythmic agents such as propranolol, digoxin, or verapamil, may be accomplished.

A recommended guideline for such a transition is given below but the physician should carefully consider the labeling instructions for the alternative agent selected.

| **Alternative Agent** | **Dosage** |
|---|---|
| Propranolol hydrochloride | 10-20 mg q 4-6 hrs |
| Digoxin | 0.125-0.5 mg q 6 hrs (p.o. or i.v.) |
| Verapamil | 80 mg q 6 hrs |

The dosage of BREVIBLOC (Esmolol Hydrochloride) should be reduced as follows:

1. Thirty minutes following the first dose of the alternative agent, reduce the infusion rate of BREVIBLOC by one-half (50%).

2. Following the second dose of the alternative agent, monitor the patient's response and if satisfactory control is maintained for the first hour, discontinue BREVIBLOC.

The use of infusions of BREVIBLOC up to 24 hours has been well documented; in addition, limited data from 24-48 hrs (N=48) indicate that BREVIBLOC is well tolerated up to 48 hours.

INTRAOPERATIVE AND POSTOPERATIVE TACHYCARDIA AND/OR HYPERTENSION
In the intraoperative and postoperative settings it is not always advisable to slowly titrate the dose of BREVIBLOC (Esmolol Hydrochloride) to a therapeutic effect. Therefore, two dosing options are presented: immediate control dosing and a gradual control when the physician has time to titrate.

1.Immediate Control

For intraoperative treatment of tachycardia and/or hypertension give an 80 mg (approximately 1 mg/kg) bolus dose over 30 seconds followed by a 150 mcg/kg/min infusion, if necessary. Adjust the infusion rate as required up to 300 mcg/kg/min to maintain desired heart rate and/or blood pressure.

2.Gradual Control

For postoperative tachycardia and hypertension, the dosing schedule is the same as that used in supraventricular tachycardia. To initiate treatment, administer a loading dosage infusion of 500 mcg/kg/min of BREVIBLOC for one minute followed by a four-minute maintenance infusion of 50 mcg/kg/min. If an adequate therapeutic effect is not observed within five minutes, repeat the same loading dosage and follow with a maintenance infusion increased to 100 mcg/kg/min (see above Supraventricular Tachycardia).

**Notes:**

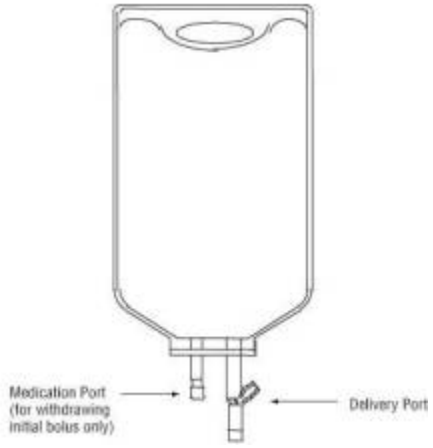
1. Higher dosages (250-300 mcg/kg/min) may be required for adequate control of blood pressure than those required for the treatment of atrial fibrillation, flutter and sinus tachycardia. One third of the postoperative hypertensive patients required these higher doses.

2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**Directions for Use of Brevibloc Premixed Injection (10 mg/mL) and Brevibloc DOUBLE STRENGTH Premixed Injection (20 mg/mL)**
This dosage form is prediluted to 100 or 250 mL to provide a ready-to-use, iso-osmotic solution of either 20 or 10 mg/mL esmolol hydrochloride in sodium chloride. It is important not to introduce additives to BREVIBLOC PREMIXED INJECTION

or BREVIBLOC DOUBLE STRENGTH PREMIXED INJECTION. See Directions for Use of the Premixed Bag for additional information.

**Directions for Use of the Premixed Bag**
**Brevibloc Premixed Injection (10 mg/mL) 250 mL IntraVia Bag**
**Brevibloc DOUBLE STRENGTH Premixed Injection (20 mg/mL) 100 mL IntraVia Bag**
BREVIBLOC PREMIXED INJECTION (10 mg/mL) and BREVIBLOC DOUBLE STRENGTH PREMIXED INJECTION (20 mg/mL) are provided in ready-to-use, non-latex, non-PVC bags with two PVC ports, a medication port and a delivery port. **The medication port is to be used solely for withdrawing an initial bolus from the bag; the medication withdrawal port is not intended for repeat bolus administration. The sterility of the premixed bag cannot be assured after repeat withdrawals from the bag. The use of aseptic technique is required when withdrawing the bolus dose. Do not add any additional medications to BREVIBLOC PREMIXED INJECTION.** Each bag is for single-patient use only and contains no preservative. It is advised that once drug has been withdrawn from BREVIBLOC PREMIXED INJECTION, the bag should be used within 24 hours, with any unused portion discarded.
The Brevibloc Premixed Injection contains Esmolol Hydrochloride at a concentration of 10 milligrams/mL. When using a 10 milligrams/mL concentration, a loading dose of 0.5 milligrams/kg infused over 1 minute period of time, for a 70 kg patient, is 3.5 mL. The loading dose can be removed from the medication port of the premixed bag.
The Brevibloc DOUBLE STRENGTH Premixed Injection contains Esmolol Hydrochloride at a concentration of 20 milligrams/mL. When using a 20 milligrams/mL concentration, a loading dose of 0.5 milligrams/kg infused over 1 minute period of time, for a 70 kg patient, is 1.75 mL. The loading dose can be removed from the medication port of the premixed bag.
**Figure 1. Two-Port IntraVia Bag**




CAUTION
Do not use plastic containers in series connections. Such use could result in an embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

TO OPEN
Do not remove unit from overwrap until ready to use. Do not use if overwrap has been previously opened or damaged. The overwrap is a moisture barrier. The inner bag maintains sterility of the solution.

Tear overwrap at notch and remove premixed bag. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

Check for minute leaks by squeezing the inner bag firmly. If leaks are found, discard solution as sterility may be impaired. Do not use unless the solution is clear, colorless to light yellow, and the seal is intact.

Fill out the patient information label supplied and apply to the inner bag.

Do not introduce additives to BREVIBLOC PREMIXED INJECTION or BREVIBLOC DOUBLE STRENGTH PREMIXED INJECTION.

PREPARATION FOR INTRAVENOUS ADMINISTRATION
(use aseptic technique)

1. Suspend premixed bag from eyelet support.

2. Remove plastic protector from delivery port at bottom of bag.

3. Attach administration set. Refer to complete directions accompanying set.

**Directions for Use of the Ready-to-use Vials**
**Brevibloc Injection (10 mg/mL) 10 mL Ready-to-use Vial**
**Brevibloc DOUBLE STRENGTH Injection (20 mg/mL) 5 mL Ready-to-use Vial**
This dosage form is prediluted to provide a ready-to-use, iso-osmotic solution of either 10 or 20 mg/mL esmolol hydrochloride in sodium chloride recommended for BREVIBLOC intravenous administration. It may be used to administer the appropriate BREVIBLOC (Esmolol Hydrochloride) loading dosage infusions by hand-held syringe while the maintenance infusion is being prepared.
The 10 mL Ready-to-use Vial contains Esmolol Hydrochloride at a concentration of 10 milligrams/mL. When using a 10 milligrams/mL concentration, a loading dose of 0.5 mg/kg infused over 1 minute period of time, for a 70 kg patient is 3.5 mL.
The 5 mL DOUBLE STRENGTH Ready-to-use Vial contains Esmolol Hydrochloride at a concentration of 20 milligrams/mL. When using a 20 milligrams/mL concentration, a loading dose of 0.5 mg/kg infused over 1 minute period of time, for a 70 kg patient is 1.75 mL.

**Directions for Use of the Brevibloc Concentrate 10 mL Ampul (250 milligrams/mL)**
**THE 2500 mg AMPUL IS NOT FOR DIRECT INTRAVENOUS INJECTION. THIS DOSAGE FORM IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED PRIOR TO ITS INFUSION. BREVIBLOC SHOULD NOT BE ADMIXED WITH SODIUM BICARBONATE. BREVIBLOC SHOULD NOT BE MIXED WITH OTHER DRUGS PRIOR TO DILUTION IN A SUITABLE INTRAVENOUS FLUID.**(SeeCompatibility Section below.)
**Dilution:** Aseptically prepare a 10 mg/mL infusion by adding two 2500 mg ampuls to a 500 mL container or one 2500 mg ampul to a 250 mL container of a compatible intravenous solution listed below. (Remove overage prior to dilution as appropriate.) This yields a final concentration of 10 mg/mL. The diluted solution is stable for at least 24 hours at room temperature. Note: The use of esmolol with propylene glycol has been associated with a higher incidence of venous irritation at concentrations greater than 10 mg/mL on continued infusion. Mixed from the ampul at concentrations of greater than 10 mg/mL BREVIBLOC has, however, been well tolerated when administered via a central vein.

**Compatibility with Commonly Used Intravenous Fluids**
BREVIBLOC was tested for compatibility with ten commonly used intravenous fluids at a final concentration of 10 mg Esmolol Hydrochloride per mL. BREVIBLOC was found to be compatible with the following solutions and was stable for at least 24 hours at controlled room temperature or under refrigeration:
- Dextrose (5%) Injection, USP
- Dextrose (5%) in Lactated Ringer’s Injection
- Dextrose (5%) in Ringer’s Injection
- Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP
- Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
- Lactated Ringer’s Injection, USP
- Potassium Chloride (40 mEq/liter) in Dextrose (5%) Injection, USP
- Sodium Chloride (0.45%) Injection, USP
- Sodium Chloride (0.9%) Injection, USP

BREVIBLOC is NOT compatible with Sodium Bicarbonate (5%) Injection, USP.

**HOW SUPPLIED**
BREVIBLOC PREMIXED INJECTION
NDC 10019-055-61, 2500 mg – 250 mL in Ready-to-use 250 mL IntraVia Bags
BREVIBLOC DOUBLE STRENGTH PREMIXED INJECTION
NDC 10019-075-87, 2000 mg – 100 mL in Ready-to-use 100 mL IntraVia Bags
BREVIBLOC INJECTION
NDC 10019-115-01, 100 mg – 10 mL Ready-to-use Vials, Package of 25
BREVIBLOC DOUBLE STRENGTH INJECTION
NDC 10019-085-01, 100 mg – 5 mL Ready-to-use Vials, Package of 10

BREVIBLOC CONCENTRATE
NDC 10019-025-18, 2500 mg – 10 mL Ampuls for Dilution, Package of 10
**Store at 25#C (77#F). Excursions permitted to 15#-30#C (59#-86#F). [See USP Controlled Room Temperature.] PROTECT FROM FREEZING.** Avoid excessive heat.
Manufactured for
**Baxter Healthcare Corporation**
Deerfield, IL 60015 USA

For Product Inquiry 1 800 ANA DRUG (1-800-262-3784)
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